



## Molecular iodine-catalyzed benzylation of arenes with benzyl alcohols

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### ABSTRACT

A novel molecular iodine-catalyzed benzylation of arenes with benzyl alcohols has been developed. The reaction can be carried out under mild conditions to afford a series of diarylmethane derivatives in high yields and good regioselectivities.

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Recently benzylation with benzyl alcohols has become an attractive method in organic synthesis.<sup>1</sup> Benzyl alcohols used as benzylating agents are preferable to benzylic halide because the formation of hydrogen halides is avoided.<sup>2</sup> Benzyl alcohols are also superior to benzyl carboxylates in benzylation because no modified substrates are involved.<sup>3</sup> In comparison with the styrene derivatives,<sup>4</sup> benzyl alcohols are more easily available. However, heavy metals are often involved in the benzylation, which results in the residue of heavy metals in the products such as pharmaceuticals. In order to avoid the metal catalysts in the benzylation, we attempted to explore non-metal catalysts to synthesize 1,1-diaryl-alkane and 1-aryl-1-heteroalkane, which are important moieties in various valuable biologically active compounds and pharmaceuticals.<sup>5</sup> To the best of our knowledge, iodine is favorable to pharmaceutical synthesis owing to its inexpensive, non-toxic, and environmental friendly characteristics. Besides, iodine can be easily removed from the reaction system. Moreover, molecular iodine is not sensitive to air or moisture. Recently iodine was employed in some nucleophilic substitution reactions.<sup>6</sup> And we have used iodine in two kinds of iodocyclization.<sup>7</sup> Herein we report a new benzylation method catalyzed by iodine without any metal catalyst.

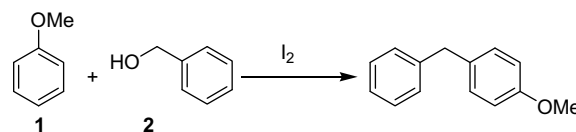
Initially, the reaction of anisole **1** with benzyl alcohol **2** was employed as a model reaction. The reaction afforded the desired product in a low yield and with a slow rate. Considering the release of stoichiometric water as a side-product, ground 4 Å molecular sieve was added into the reaction mixture to remove water from

the reaction system so as to promote the reaction. Subsequently, the optimal reaction conditions, such as catalyst loading and reaction temperature, were screened. The experimental results are listed in Table 1.<sup>10</sup> The best result was obtained with 10 mol % of molecular iodine and 10 mg of ground 4 Å molecular sieve at 60 °C.

Following the optimization of the reaction conditions, we examined the benzylation of different arenes with primary benzyl alcohol (Table 2). As shown in Table 2, electron-rich arenes such as anisole, toluene, *o*-xylene, *m*-xylene, *p*-xylene, 1,2,3,4-tetrahydronaphthalene and arenes bearing phenolic hydroxyl and mercapto groups were tested, and all of them reacted smoothly with benzyl alcohol to give the corresponding benzylation products in good yields after short reaction time (4 h). The *para*-substituted product

**Table 1**

Reaction of anisole and benzyl alcohol in the presence of 4 Å molecular sieve<sup>a</sup>



Entry	Cat. (mol %)	Temperature (°C)	Time (h)	Yield <sup>b</sup> (%)
1	20	100	4	89
2	20	80	4	88
3	20	60	4	88
4	10	60	4	87
5	10	25	8	45
6	5	60	8	66

<sup>a</sup> Reactions were carried out with **1** (1.1 mmol) and **2** (1 mmol) in the presence of ground 4 Å molecular sieve (10 mg).

<sup>b</sup> Isolated yield based on the amount of **2**.

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**Table 2**  
Reaction of arenes with benzyl alcohol<sup>a</sup>

Entry	Arene	Major product	Yield <sup>b</sup> (%)	Selectivity <sup>c</sup>
1			88	62:38
2			70	59:41
3			76	74:36
4			72	85:15 <sup>d</sup>
5			65	—
6			60	68:32
7			75	67:33 <sup>e</sup>
8			68	— <sup>f</sup>

<sup>a</sup> Reactions were carried out with iodine (10 mol %), **1** (1.1 mmol) and **2** (1 mmol) in the presence of ground 4 Å molecular sieve (10 mg) at 60 °C for 4 h.

<sup>b</sup> Isolated yield based on the amount of benzyl alcohol.

<sup>c</sup> Regioselectivity was determined by <sup>1</sup>H NMR or <sup>13</sup>C NMR spectroscopic data, ratio = *p*-:*o*-product.

<sup>d</sup> Ratio = 1-(2,4-dimethylbenzyl) benzene: 2-benzyl-1,3-dimethylbenzene.

<sup>e</sup> Ratio = 2-benzyl-4-methylphenol:3-benzyl-4-methylphenol.

<sup>f</sup> Almost only 2-benzyl-4-methylbenzenethiol.

was obtained as the major product (Table 2, entries 1, 2, 3, 4 and 6). As for the reaction of *m*-xylene (Table 2, entry 4), 2-benzyl-1,3-dimethylbenzene, another isomer of the main product, was also obtained in spite of the strong steric hindrance from two methyl groups. However, when *p*-cresol and 4-methylbenzenethiol were used as reaction substrates, 2-benzyl-4-methylphenol and 2-benzyl-4-methylbenzenethiol were provided as the main products, respectively. This is the first example of benzylation of mercapto group-containing substrate to give corresponding arylation product.

In Table 3, different primary benzyl alcohols are employed in the benzylation of anisole. Both electron-rich (Table 3, entries 1–3) and electron-poor primary benzyl alcohols (Table 3, entries 5–8) could react with anisole smoothly to afford the corresponding diarylmethanes in high yields. In all cases, the corresponding products were obtained with excellent selectivities (99:1). As for secondary benzyl alcohols, so far, there were only a few successful reports about the employment of the secondary benzyl alcohols bearing β-H atom as the benzylation substrates.<sup>1f,4e,8</sup> Under our conditions, the secondary benzyl alcohols can undergo the benzylation to afford the desired benzylation products (Table 4). For instance, the reaction of 1-phenylethanol with anisole catalyzed by molecular iodine gave the corresponding product in 90% yield, and the ratio of *p*-:*o*-product was 87:13 (Table 4, entry 1). Other secondary benzyl alcohols produced the corresponding benzylation products in good yields and with excellent selectivity of *p*- versus *o*-product (99:1). However, when 1-phenylethanol was employed as an alkylating agent in the benzylation under Brønsted or Lewis acid-catalyzed conditions, styrene was detected as the major product.<sup>4a,9</sup> This indicated that the molecular iodine-catalyzed benzylation was an efficient benzylation involving secondary benzyl alcohols as reaction substrates.

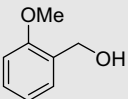
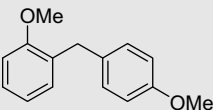
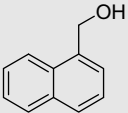
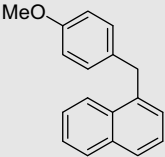
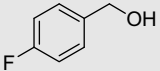
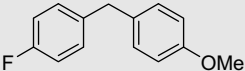
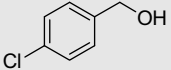
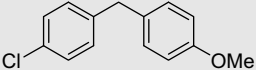
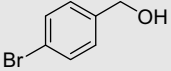
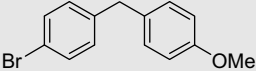
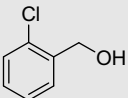
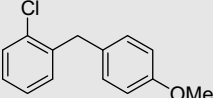
Based on the above experimental results, we proposed a possible reaction mechanism for this molecular iodine-catalyzed benzylation, as shown in Scheme 1. A benzyl carbocation **2** might be formed from benzyl alcohol **1** in the presence of molecular iodine, and then **2** could be attacked by arenes to afford the corresponding product **3**.

In summary, we have developed an efficient iodine-catalyzed benzylation of arenes with benzyl alcohols in the presence of 4 Å molecular sieve. Compared to previous benzylation reactions, metal catalysts were avoided in this new method. The reaction can tolerate water and air. Advantages such as mild reaction conditions, short reaction time, broad substrate scope, and simple work-up render this transformation a practical route to the valuable 1,1-diarylmethanes.

**Table 3**  
Reaction of primary benzyl alcohols with anisole<sup>a</sup>

Entry	Benzyl alcohol	Major product	Yield <sup>b</sup> (%)	Selectivity <sup>c</sup>
1			81	99:1
2			80	99:1

**Table 3** (continued)

Entry	Benzyl alcohol	Major product	Yield <sup>b</sup> (%)	Selectivity <sup>c</sup>
3			78	99:1
4			75	99:1
5			85	99:1
6			88	99:1
7			87	99:1
8			80	99:1

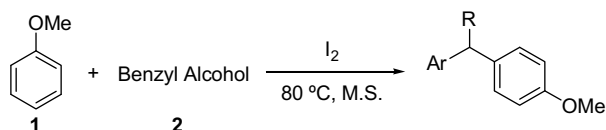
<sup>a</sup> Reactions were carried out with iodine (10 mol %), **1** (1.1 mmol) and **2** (1 mmol) in the presence of ground 4 Å molecular sieve (10 mg) at 60 °C for 4 h.

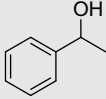
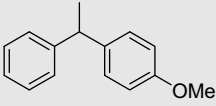
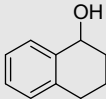
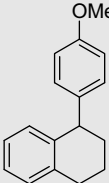
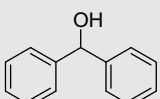
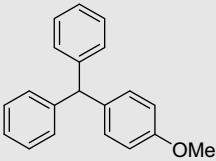
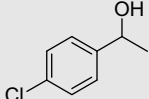
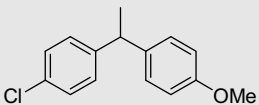
<sup>b</sup> Isolated yield based on the amount of benzyl alcohol.

<sup>c</sup> Regioselectivity was determined by <sup>1</sup>H NMR or <sup>13</sup>C NMR spectroscopic data, ratio = *p*–:*o*–product.

**Table 4**

Reaction of secondary benzyl alcohols with anisole<sup>a</sup>



Entry	Benzyl alcohol	Major product	Yield <sup>b</sup> (%)	Selectivity <sup>c</sup>
1			90	87:13
2			65	99:1
3			60	99:1
4			91	99:1

(continued on next page)

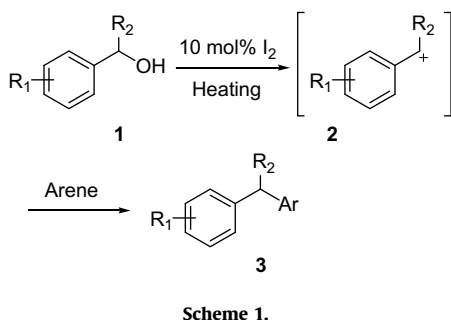
Table 4 (continued)

Entry	Benzyl alcohol	Major product	Yield <sup>b</sup> (%)	Selectivity <sup>c</sup>
5			72	99:1
6			88	99:1

<sup>a</sup> Reactions were carried out with iodine (10 mol %), **1** (1.1 mmol) and **2** (1 mmol) in the presence of ground 4 Å molecular sieve (10 mg) at 80 °C for 6 h.

<sup>b</sup> Isolated yield based on the amount of benzyl alcohol.

<sup>c</sup> Regioselectivity was determined by <sup>1</sup>H NMR or <sup>13</sup>C NMR spectroscopy and comparison with literature data, ratio = *p*-*o*-product.



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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.146.

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- Typical procedure of iodine-catalyzed benzylation of anisole and benzyl alcohol:** A 10-ml round-bottomed flask, fitted with a reflux condenser, was charged with I<sub>2</sub> (0.05 mmol, 10 mol %), benzyl alcohol (0.5 mmol), anisole (0.55 mmol), and 10 mg of ground 4 Å molecular sieve. The mixture was heated at 60 °C for 4 h, cooled down, and treated with aqueous Na<sub>2</sub>O<sub>3</sub>, then extracted three times with ethyl acetate. The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure; the resulting crude mixture was purified by column chromatography on silica gel to afford the product.